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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/073,464	02/11/2002	James Tiedje	MSU-06787	4392

7590 07/01/2005

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EXAMINER	
BAUSCH, SARAE L	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/073,464	TIEDJE ET AL.	
	Examiner	Art Unit	
	Sarae Bausch	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/07/2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The examiner reviewing your application at the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to examiner Sarae Bausch.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/07/2005 has been entered.

Status of Claims

2. This action is in response to papers filed 04/07/2005 in which claim 1 was amended. Claims 1-15 are pending and claims 16-21 are canceled. New grounds of rejection are set forth below. **This action is Non-Final.**

New Grounds of Rejection

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had

possession of the claimed invention. Newly amended claim 1 with the recitation of "in a single step" is not supported in the specification and raises the issue of new matter. The specification teaches genomic DNA from test strains labeled by random priming and co-hybridized to the chip with reference DNA on page 6, lines 23-25. The specification exemplifies a multiple step procedure to produce a hybridizaiton pattern. The specification exemplifies arrays prehybridized in pre-hybridization buffer for 20 min at 65°C, hybridized with approximately 1μg of Cy3- and Cy5- labeled DNA mixture in hybridization overnight and washed with primary wash buffer and twice with secondary wash buffer on page 33, lines 17-22. The specification does not teach a single step to produce a hybridization pattern. The specification provides no indication of the criticality of using only a single step to produce a hybridization pattern (single step of hybridizing the DNA without any addition steps, such as a prehybridization step or washing step). There is no support in the specification to use a method of producing a hbyridiziation pattern on an arrayed element in a single step. As discussed in MPEP 2163.05, section II, the introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 1-15 are rejected under 35 U.S.C. 102(e) as being anticipated by Straus (US 2002/0086289 A1 [published 7/2002; filed 6/1999]), as evidenced by DeRisi et al (Science 278:680-686 [10/1997]).

Straus discloses a method for identifying bacteria in which labeled target DNA from a test sample including bacteria is hybridized to a "detection ensemble" of detection sequences from 5 or more distinct genomes arrayed on a solid support (see entire reference, particular pages 3-4 and the definition of "minimum genomic derivation" at pages 7-8). Straus teaches that in embodiments of his invention, the detection sequences arrayed on a solid support are amplified genomic DNAs (see, e.g., page 17, right column). Straus further discloses both the combination of positive and negative control probes with test sample molecules prior to hybridization (see, e.g., page 19), and preparation of a database of fingerprints with which test sample patterns may be compared (see, e.g., page 28). Regarding the step of co-hybridizing said target and reference DNA to said arrayed elements in a single step to produce a hybridization pattern, Straus teaches hybridizing the amplified selected ID probes to a detection array without additional steps (addressable array comprising an ensemble of detection sequences) (see paragraph 362). Regarding the step of "calculating hybridization signal intensity ratio at each array element," it is noted that Straus states that "Microarrays are scanned with a laser fluorescent scanner, and signals are processed and recorded as is described in published reports," referring to the DeRisi et al reference (page 25). The DeRisi et al reference discloses that processing and recording of signals comprises calculation of a hybridization signal intensity ratio (see entire reference,

particularly footnote 49). Accordingly, it is an inherent property of the method disclosed by Straus that it includes such a step, and therefore Straus anticipates the instant claims.

Regarding claims 5 and 9-15, it is further noted that the solid supports disclosed by Straus include microchips (see, e.g., page 10). Regarding claims 2-4 and 10-12, it is noted that the samples disclosed by Straus include samples from a test subject, samples comprising pathogens, and environmental samples (see pages 4, 10, and 12). Regarding claim 6, the processing disclosed by DeRisi et al comprises statistical analysis (see footnote 49 of DeRisi et al).

Response to Arguments

On page 6, first paragraph of the response mailed 04/07/2005, the response traverses the rejection because Applicants claim does not anticipate each and every element as set forth in their claim is not expressly or inherently described in a single prior art reference. The applicants assert that Straus does not teach providing both labeled target DNA and labeled reference DNA. This response has been thoroughly reviewed but not found persuasive. Strauss does teach the simultaneous hybridization of labeled target and labeled reference DNA in a single step as exemplified in step 7 (see figure 5) (paragraphs 230-232). Strauss teaches amplified ID probes, which comprise target and reference DNA, are labeled and further identified by hybridization to a two dimensional detection array of ID probe ensembles as in step 3 (see paragraph 0145 and 149) and figure 5, last step. Strauss teaches that the ID probe ensembles attached to the two-dimensional detection array are amplified prior to attachment to the array (see paragraph 0195, claim 35, page 34 and paragraph 362). Furthermore, in figure 5, Strauss exemplifies the first hybridization step comprising hybridizing the sample on the array to an ensemble of probes, including ID probe, in a single step (test and reference samples) and teaches the probes halves

consists of an inner portion that corresponds to adjacent parts of an ID sequence and the outer portion of the probe comprises an amplification sequence (nucleic acid label) (see paragraphs 182 and 183). Therefore, Strauss et al. does teach labeled reference and labeled target DNA co hybridized to arrayed elements in a single step. Furthermore, as stated in the MPEP 2111.03, "The transitional phrases "comprising", "consisting essentially of" and "consisting of" define the scope of a claim with respect to what unrecited additional components or steps, if any, are excluded from the scope of the claim. The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., Invitrogen Corp. v. Biocrest Mfg., L.P., 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 2003) ("The transition comprising' in a method claim indicates that the claim is open-ended and allows for additional steps.")" Therefore, the instant pending claims do not exclude additional method steps and the method of identifying bacteria is not limited to only the steps recited in the claims. Straus teaches all the limitations recited in present claims 1-15, and therefore this rejection is maintained.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-5, 7-13, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuiper et al. (Current Opinion in Biotechnology, 1999, 10:511-516) and Greisen et al. (J.Clin. Microbial. 1994, vol. 32, pp 335-351).

Kuiper et al. teaches producing a specific DNA array for the rapid identification of pathogens and spoilage bacteria (instant claim 3-4, 11-12) (see page 512, 2nd column, 2nd paragraph). Kuiper et al. teaches producing microarrays by spotting amplicon of each ORF annotated in the genome sequence of interest on a defined support material, preferably glass-slides. Kuiper et al. teaches fluorescently labeled cDNA is used for hybridization to the DNA arrays and signal detection by confocal laser scanning (instant claim 7 and 11) (see page 512, 2nd column, 1st paragraph). Kuiper further exemplifies that different cDNA strains can be differentially labeled and used in one combined sample for hybridization providing the possibility of multiplexing and allowing for several different cDNA samples (see page 512, 2nd column, 1st paragraph). Kuiper et al. does not teach the use of at least four strains of reference bacterial species.

Greisen et al. teaches a method of detecting DNA for the identification of over 60 different strains representing 18 different bacterial species found as pathogens (instant claim 3 and 11) or presumptive contaminants in human CSF (see page 336, 1st column, 1st paragraph). Greisen et al. exemplifies amplifying DNA, followed by gel electrophoresis of amplified products, and blotting the gel onto a Pall Biodyne membrane and fixing the DNA to the membrane by a UV crosslinker (amplified genomic DNA arrayed on a solid support, microchip) (instant claim 5) (see page 336, 1st column, last paragraph cont'd to 2nd column). Greisen et al. teach probes of target DNA and reference DNA labeled with ^{32}P (see probe hybridization, page

338 and table 3) and hybridization of target DNA probes and reference DNA probes hybridized to DNA blots in 5xSSPE. Greisen et al. teach up to 12 meningitis and contaminant probes (reference and test DNA) tested against seven major bacterial species causing meningitis and identification of bacteria in CSF based on the hybridization pattern of each probe (instant claim 8 and 13) (see page 346, 2nd column, last two paragraph and table 4). Greisen et al. teaches that the use of the panel of probes would enable a single CSF sample to obtain multiple probe hybridization results and form a more rapid and sensitive means of detecting bacteria in clinical samples (see page 350, 1st column, last paragraph). Greisen et al. does not teach co-hybridizing target and reference DNA in a single step or the use of fluorescence detection for hybridization.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have improved the method of identification of pathogens using fluorescently labeled cDNA probes as taught by Kuiper et al. to include the testing of at least seven bacterial species causing meningitis by using up to 12 meningitis and contaminant probes as taught by Greisen et al. The ordinary artisan would have been motivated to use multiple probes, comprising up to 12 meningitis and contaminant probes as taught by Gresien et al. in the DNA microarray method taught by Kuiper et al. because Kuiper et al. suggests using different cDNA strains differentially labeled to be used in one combined sample for hybridization. Furthermore, the ordinary artisan would have had a reasonable expectation of success that using up to 12 different probes to test against seven major bacterial species that cause meningitis could be used in the method of Kuiper et al. because Kuiper et al. suggests using different cDNA strains in one sample for multiplexing and allowing for analysis of several different cDNA samples at one time.

Furthermore, it would have been prima facie obvious to improve the method of detection of bacteria in a sample using southern blot hybridization as taught by Greisen et al. to include co hybridization of probes in one combined sample and fluorescence detection hybridization as taught by Kuiper et al. The ordinary artisan would have been motivated to improve the method of the southern blot hybridization method as taught by Greisen et al. to include a more rapid, automated method of multiplexing for the identification of pathogens in bacteria as taught by Kuiper et al. because Kuiper et al. suggests using different multiple labeled probes for combining several different cDNA sample for the possibility of multiplexing. Furthermore, the ordinary artisan would be motivated to use fluorescent-labeled probes to eliminate the use of radioactivity, as fluorescence in non-radioactive. The ordinary artisan would have had a reasonable expectation of success that the use of fluorescent-labeled probes to detect pathogens could be used in the method of Greisen et al. because Kuiper et al. teach the use of fluorescent-labeled probes hybridizing to a sample for the detection of pathogens. The ordinary artisan would have had a reasonable expectation of success that the use of co hybridizing probes in a single step could be used in the method of Greisen et al. because Greisen et al. teaches the use of panel of probes that would enable the use of a single CSF sample to obtain multiple probe hybridization results and form a more rapid and sensitive means of detecting bacteria in clinical samples.

7. Claims 6 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuiper et al. (Current Opinion in Biotechnology, 1999, 10:511-516) and Greisen et al. (J.Clin. Microbial. 1994, vol. 32, pp 335-351) as applied to claims 1-5, 7-13, and 15 above, and further in view of Arfin et al.. (J. Biol. Chem. 2000, vol. 275, pp. 29672-29684).

The method of Kuiper et al. and Greisen et al. is set forth in section 6 above. Kuiper et al. and Greisen et al. do no teach statistical analysis in calculating the target signal to reference signal hybridization ratio at each array element.

Arfin et al. teach replication and appropriate statistical analysis is required for determining the accuracy of DNA microarray measurements. Arfin et al. teach that thousands of measurements are obtained from a single experiment using DNA microarrays experiments and in order to interrupt data from experiments it is necessary to employ statistical methods capable of distinguishing chance occurrences from biologically meaningful data (see page 29676, 1st column, last paragraph). Arfin et al. teach using a t test to evaluate the difference between the means of two groups employing the variance within groups as an error term. Arfin et al. teach using the t test to determine statistical differences among different filters hybridized with the same RNA of the same genotype as well as differences among different RNA preparations of the same genotype hybridized to the same filters (see page 29674, 2nd column, 3rd paragraph).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of Kuiper et al. and Greisen et al. of identifying bacteria using a microarray to include statistical analysis of the data as taught by Arfin et al. The ordinary artisan would have been motivated to improve the method of Kuiper et al. and Greisen et al. to include statistical analysis of the data obtained by the microarray analysis because Arfin et al. teach replication and appropriate statistical analysis is required for determining the accuracy of DNA microarray measurements. Furthermore Arfin et al. teach that thousands of measurements are obtained from a single experiment using DNA microarrays experiments and in order to interrupt data from experiments it is necessary to employ statistical

methods capable of distinguishing chance occurrences from biologically meaningful data, therefore, the ordinary artisan would have had a reasonable expectation of success of using statistical data analysis in the method of Kuiper et al. and Greisen et al.

Conclusion

No claims allowable over the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 10am-7pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (571) 272-0745. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jehanne Sitton

JEHANNE SITTON
PRIMARY EXAMINER
6/24/05

Sarae Bausch, PhD.
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